REMARKS

Claims 1-2 and 11 have been cancelled. Claim 6 has been amended. Claims 3-10 are now pending in this application. Support for the amendments is found in the existing claims and the specification as discussed below. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Telephonic interview

Applicant's representative would like to thank Examiner Chong for the courtesy of a telephonic interview on August 28, 2007 which is summarized on page 4.

Rejection under 35 U.S.C. § 103(a) (Sirois, Peichev, Majka, Schmeisser)

Claims 3-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Sirois, G. (US 2003/0186920) in view of Peichev, et al. (IDS 7/22/04), Majka, et al. (PTO Form 892, 12/19/05) and Schmeisser, et al. (Cardiovascular Research, 2001, 49: 671-680).

The Examiner asserts that Sirois teaches a method of testing binding of an antisense compound to VEGF and monitoring formation of new capillary vessels. Although Sirois does not teach prominin-1, the Office Action asserts that Peichev, et al. teach CD34+ cells that co-express AC133 (prominin-1); Majka, et al. teach antisense oligomers that downregulate expression of AC133 (prominin-1); and Schmeisser, et al., referring to Peichev, et al. teach that CD34+ cells coexpress AC133 along with VEGFR-2 and constitute functional endothelial precursors.

It is well accepted that a *prima facie* case of obviousness requires that three basic criteria be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed invention and the reasonable expectation of success must both be found in the prior art, and must not be based on Applicants' disclosure.

The above criteria have been recently modified by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 82 U.S.P.Q.2d 1385 (2007). Although the United States Supreme Court rejected a "rigid application" of the teaching-suggestion-motivation test for obviousness, the Court nevertheless emphasized (at p.14) that a finding of obviousness requires an "apparent reason to combine the known elements in the fashion claimed by the patent at issue."

Applicants assert that the above criteria have not been met.

There is no apparent reason to combine the cited references. While Sirois teaches identification of antisense oligonucleotides of VEGF receptors and screening for successful antisense oligonucleotides by monitoring reduced blood vessel formation (paragraph 0104 of Sirois), Sirois is completely silent regarding prominin-1. While Peichev, et al., Majka, et al. and Schmeisser, et al. relate to studies that include prominin-1 (AC133), there is nothing in any of these references that would cause one of ordinary skill in the art to use prominin-1 in a screening method, specifically to interchange the VEGF taught by Sirois for prominin-1. Accordingly, there is no apparent reason to use prominin-1 in an assay to determine binding to prominin-1 protein or hybridization to a nucleic acid corresponding to prominin-1 to screen for molecules that affect pathological angiogenesis.

Peichev, et al. teach that both prominin-1 and VEGF are found on CD34+ cells and that CD34+ cells have a role in angiogenesis. However, the reference does not teach a role for prominin-1 in angiogenesis. In fact, Peichev, et al. teach that the function of AC133 is unknown (Peichev, et al., page 953, col. 1, para. 4, lines 3-5). Majka, et al. teach antisense deoxyoligonucleotides, but do not teach a role for prominin-1 in angiogenesis. Schmeisser, et al. merely refer to Peichev, et al. Indeed, Schmeisser, et al. offer evidence that the presence of a given marker on cells with endothelial potential does not suggest a role for the marker in achieving the cells' endothelial phenotype. For example, while the endothelial precursors of Peichev, et al. are CD34+, those of Schmeisser, et al. are CD34-. Hence, CD34 is apparently not required for endothelial differentiation, despite the fact that it was expressed by the endothelial precursors of Peichev. Similarly, the expression of AC133 by the endothelial precursors of Peichev, et al. cannot directly suggest that AC133 would effect the endothelial fate of cells.

In addition, while the endothelial precursors of Peichev were AC133+, the mature endothelial cells obtained were AC133 negative (Peichev, et al., Abstract: Schmeisser, et al. page 672, col. 1, last paragraph). Accordingly, the combination of references does not teach or suggest a role for AC133 (prominin-1) in angiogenesis, particularly pathological angiogenesis.

Majka, et al. employ an anti-AC133 antibody to detect AC133 expression on CD34+ cells derived from bone marrow by FACS. However, this antibody is not tested for any effects on any cells to which it might bind. Regarding the use of antisense oligodeoxynucleotides, when Majka, et al. downregulate AC133 in the CD34+ cells using antisense oligodeoxynucleotide, no effects whatsoever are observed (see Majka, et al. page 61, col. 1, lines 1-6). Accordingly, Majka, et al. merely conclude that AC133 is expressed in human cord blood, bone marrow progenitor cells, and some tumor cell lines, and that disruption of expression does not effect normal cell development (page 62, last paragraph). Accordingly, there is no apparent reason to combine the teaching of Majka, et al. with the teaching of Sirois to screen for molecules that inhibit the expression and/or activity of prominin-1 in order to identify molecules for the treatment of pathological angiogenesis as Majka, et al. were unable to characterize any role for prominin-1 and are silent regarding any role that prominin-1 might play in pathological angiogenesis.

Similar to Majka, et al. Peichev, et al. use anti-AC133 antibody to detect a subpopulation of circulating CD34+ cells (page 955). While this CD34+ subpopulation is identified as having possible relevance for postnatal angiogenesis (page 957, col. 2, esp. last paragraph), Peichev, et al. do not teach or suggest a direct involvement of AC133 in angiogenesis.

While Peichev, et al. teaches that AC133+ is a marker for a particular subset of CD34+ cells, and that these cells may be involved in neoangiogenesis, there is no teaching that an agent that binds to AC133 or hybridizes to a nucleic acid encoding AC133 will have potential for the treatment of pathological angiogenesis. Peichev, et al. disclose binding of antibodies to AC133 merely to determine the number of AC133+ cells by FACS analysis. There is no recognition in Peichev, et al of the potential of AC133 to screen for agents that can be used to treat pathological angiogenesis. There is no teaching that drugs which bind to AC133 can be used to treat pathological angiogenesis. Peichev, et al. do not teach monitoring of pathological angiogenesis upon administration to a patient of molecules that either bind to prominin-1 (AC133) or to a nucleic acid encoding prominin-1. Accordingly, as the combination of references does not teach

or suggest a role for AC133 (prominin-1) in angiogenesis, particularly pathological angiogenesis, there is no apparent reason to combine Peichev, et al, Majka, et al. and /or Schmeisser, et al. with Sirois.

Furthermore, the cited references do not provide a reasonable expectation of success. As discussed above, none of the cited references directly implicate prominin-1 (AC133) in angiogenesis. Peichev et al. teach CD34+ cells express VEGFR-2 and AC133 (prominin-1). However, the mere presence of AC133 in CD34+ cells along with CD34 and VDGFR-2 and numerous other proteins does not teach or suggest that AC133 would itself be involved in angiogenesis. There is no reference in Peichev, et al. or any of the cited references on a role for prominin-1 in angiogenesis. The Examiner also cites Schmeisser, et al. as teaching that "this finding allows for the potential of therapeutic management in patients with pathological angiogenesis (see page 680, last paragraph)". However, Schmeisser, et al. make no statements whatsoever regarding pathological angiogenesis. Schmeisser, et al. conclude that "the salient finding of the present study is that monocytes (CD34-/CD14+) or a subfraction of monocytes have the potential to coexpress very specific endothelial markers and mono-/macrophagocytic antigens under growth factor stimulation in vitro" Schmeisser, et al., page 767, col. 1, first sentence under "4. Discussion". The passage cited by the Examiner (page 680, last paragraph) states that "the significance of the above phenomena in angiogenesis is ***quite speculative***...(emphasis added)". It is not apparent how this teaching can be used as a basis for rejecting claims directed to screening for molecules binding to prominin-1 to provide inhibitors of pathological angiogenesis.

Furthermore, the claim 6 has been amended to "...monitoring a reduction in the number of blood vessels during progression of a disease when administering said molecules, thereby identifying molecules for the treatment of pathological angiogenesis without affecting normal vascular development." None of the references teach that prominin-1 is involved directly in angiogenesis and none of the cited references teach that prominin-1 is specifically involved in "pathological angiogenesis without affecting normal vascular development" as now claimed. Support for the amendment is found in Example 1 on page 11, line 17. This element is not taught by any of the cited references. Indeed, Sirois teaches that "VEGF plays a pivotal role in the regulation of ***normal*** and pathophysiological angiogenesis" (paragraph 0005, emphasis

added). Sirois does not teach "a method of screening for molecules for the treatment of pathological angiogenesis without affecting normal vascular development" as claimed. As discussed above, this deficiency is not corrected by the secondary references because none of the references teach a role for prominin-1 in pathological angiogenesis or even in angiogenesis generally. At best, the cited references suggest a role for CD34+ cells in angiogenesis, but not AC133 (prominin-1) per se.

In view of Applicants' arguments and amendments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a) (Sirois, Peichev, Majka, Schmeisser, Babinet, Murphy)

Claims 3-10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Sirois, G. (US 2003/0186920) in view of Peichev, et al. (IDS 7/22/04), Majka, et al. (PTO Form 892, 12/19/05) and Schmeisser, et al. (Cardiovascular Research, 2001, 49: 671-680) as applied to claims 3-6 above, and further in view of Babinet, et al. (an Acad. Bras. Cienc. 2001) and Murphy (US 2003/0045489)..

Regarding claims 3-6, the arguments presented above are incorporated here. It is respectfully submitted that Sirois, Peichev, et al., Majka, et al., and Schmeisser, et al., taken separately or together, fail to teach or suggest the present claim limitations.

Claims 7-10 depend from claim 6 and are also believed to be patentable, at least because they include all of the limitations of claim 6.

Babinet, et al. and Murphy, et al are relied upon to show the use of knockout mouse models which pertains to claims 7-10. However, neither Babinet, et al nor Murphy, et al teach a knock out mouse or other mammal that does not express prominin-1. Accordingly, neither Babinet, et al. nor Murphy, et al. correct the defects of the references discussed above.

None of the cited references teach administration of prominin-1 antagonists in a model of pathological angiogenesis. Moreover, because the role of AC133 *as such* in pathological angiogenesis is not disclosed and not suggested in any of the cited references, there was no motivation for one of ordinary skill in the art to administer such molecules in a model of pathological angiogenesis at the time of the claimed invention.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: Aug 28, 2007

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